Remarks

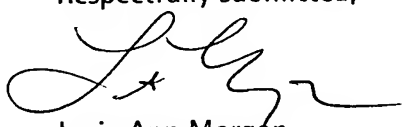
Currently Claims 20-114 are pending.

Claims 20, 32, 35 and 36 have been amended. Claims 20 and 36 have been amended to change plural to singular. No new matter is added. Claim 32 has been amended to change "ethanesulphonate" to "methanesulphonate". Support for this claim amendment can be found throughout Applicants' original specification and particularly at page 9, lines 34-35 and Example 36. No new matter is added. Claim 35 has been amended to place the claim in standard US format. No new matter is added.

New claims 39-114 have been added. New claims 39-61 are directed toward methods of treating a depressive state. New claims 62-78 are directed toward methods of treating anxiety. New claims 79-95 are directed toward methods of treating a panic disorder. New claims 96-113 are directed toward methods of treating a gastrointestinal disorder. New claim 114 is directed toward a specific compound. Support for new claims 39-95 can be found throughout Applicant's original specification, including at original claims 1, 10-14 and 18, the examples, at page 11, lines 8-24 and page 14, line 8 through page 15, line 13. Support for new claims 96-113 can be found throughout Applicant's original specification, including at original claims 1, 10-14 and 18, the examples and at page 13, lines 33-34 and page 14, lines 28-30. No new matter is added. Support for claim 114 can be found in Applicants' original specification, including at Example 37.

Applicants respectfully submit that the instant application is in condition for substantive examination, which action is respectfully requested. The Examiner is invited to contact the undersigned at 483-8222, to discuss this case, if desired.

Respectfully submitted,



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At page 3, lines 12-14, please amend the paragraph to read:

--It will be appreciated by those skilled in the art that the compounds of formula (I) contain at least one chiral centre (namely the carbon atom show as * in formula (I)).—

At page 6, lines 10-14, please amend the paragraph to include appropriate subscripts as follows:

--When R_4 is $(CH_2)_qR_7$ or $(CH_2)_rCO(CH_2)_pR_7$, R_7 is suitably hydrogen, hydroxy, NR_9R_8 e.g. NH_2, $NH(C_{1-4}$ alkyl) e.g. NH methyl or $N(C_{1-4}$ alkyl$)_2$ e.g. N(methyl)$_2$, $NH(C_{1-4}$ alkyl$)NH_2$ e.g. NH(ethyl)NH_2, $NH(C_{1-4}$ alkyl) wherein q is 1 or 2 and both p and r are independently zero or an integer from 1 to 2.--

At page 25, lines 24-26, please amend the paragraph to read:

--Compounds of formula (V), (VI), ~~(VI),~~ (VIII), (IX), (X) ,(XII), (XIII) or (XIV) may be prepared by analogous methods to those used for known compounds.--

At page 39, lines 28-33, please amend the title to add a common at line 31 between "A" and "B" as follows:

--Intermediate 22

4-{[1-(3,5-Bis-trifluoromethyl-phenyl)-ethyl]-methyl-carbamoyl}-3-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid benzyl ester (mixture of enantiomers A,B) (22a)

4-{[1-(3,5-Bis-trifluoromethyl-phenyl)-ethyl]-methyl-carbamoyl}-3-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid benzyl ester (mixture of enantiomers C,D)(22b).--

At page 48, lines 20-26, please amend the title at line 24 to change "4-{[1-(S)-" to "4-{[1-(R)-" as follows:

--Intermediate 38

4-{[1-(S)-(3,5-Bis-trifluoromethyl-phenyl)-ethyl]-methyl-carbamoyl}-3-(S)-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid 1-(R)-phenyl-ethyl ester (diastereomer 1) (38a)

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4-{[1-(SR)-(3,5-Bis-trifluoromethyl-phenyl)-ethyl]-methyl-carbamoyl}-3-(R)-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid 1-(R)-phenyl-ethyl ester (diastereomer 2) (38b)--

At page 50, lines 20-24, please amend the titled to remove the "-" before "40b" as follows:

--Intermediate 40

2-(S)-(4-Fluoro-2-methyl-phenyl)-3-oxo-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide (40a)

2-(S)-(4-Fluoro-2-methyl-phenyl)-3-oxo-piperazine-1-carboxylic acid [1-(S)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide.(-40b).—

At page 62, lines 4-11, please amend the paragraph to read:

--TEA (700 μL) and diphenyphosphorylazide (812 μL) were added to a solution of intermediate 59 (400 mg) in dry toluene (20 mL) previously cooled to 0°C under a nitrogen atmopshere. The solution was stirred at r.t. for 3 hr, then 400 mg~~}~~ of intermediate 63 was added and the mixture was heated to 100°C for 1 hr. The mixture was allowed to cool to r.t. and partitioned between water and AcOEt. The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 8:2) to give the title compound 64a (340 mg) and the title compound 64 b (250 mg).--

At page 81, lines 1-3, please amend the title at line 24 to change "...carboxylic acid [1-(S)-(3,5)-..." to read "...carboxylic acid [1-(R)-(3,5)-..."as follows:

--Example 17

(+)-2-(R)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(SR)-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide hydrochloride--

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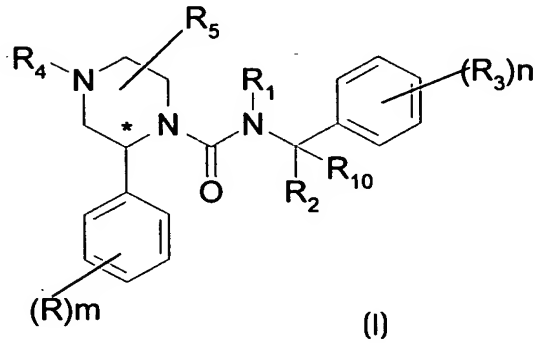
20. (Amended) A compound of formula (I)



(I)

wherein

R is a halogen atom or a C_{1-4} alkyl group;

R_1 is hydrogen or a C_{1-4} alkyl group;

R_2 is hydrogen, a C_{1-4} alkyl, C_{2-6} alkenyl or a C_{3-7} cycloalkyl group; or R_1 and R_2 together with nitrogen and carbon atom to which they are attached respectively are a 5-6 membered heterocyclic group;

R_3 is a trifluoromethyl, a C_{1-4} alkyl, a C_{1-4} alkoxy, a trifluoromethoxy, or a halogen group;

R_4 is hydrogen, a $(CH_2)_qR_7$ or a $(CH_2)_rCO(CH_2)_pR_7$ group;

R_5 is hydrogen, a C_{1-4} alkyl or a COR_6 group;

R_6 is hydrogen, hydroxy, amino, methylamino, dimethylamino, a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen or a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms;

R_7 is hydrogen, hydroxy or NR_8R_9 wherein R_8 and R_9 are independently hydrogen or C_{1-4} alkyl optionally substituted by hydroxy, or by amino;

R_{10} is hydrogen, a C_{1-4} alkyl l group or

R_{10} together with R_2 is a C_{3-7} cycloalkyl group;

m is zero or an integer from 1 to 3; n is zero or an integer from 1 to 3; both p and r are independently zero or an integer from 1 to 4; q is an integer from 1 to 4; provided that , when R_1 and R_2 together with nitrogen and carbon atom to which they are attached respectively are a 5 to 6 membered heterocyclic group, l) m is 1 or 2; ii)

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when m is 1, R is not fluorine and iii) when m is 2, the two substituents R are not both fluorine,

~~and~~ or a pharmaceutically acceptable ~~salts and solvates~~ salt or solvate thereof.

32. (Amended) 2-(S)-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide ~~ethanesulphonate~~ methanesulphonate.

35. (Amended) A method for the treatment of ~~a mammal, in particular in the treatment of conditions~~ a condition mediated by ~~tachykinins~~ a tachykinin, in a mammal, said method comprising ~~administration of~~ administering an effective amount of a compound as claimed in ~~of any claims 20 to 33~~ claim 1.

36. (Amended) The method of Claim 35 wherein said ~~tachykinins~~ tachykinin is substance P or other neurokinins.